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Appeal Brief

In the United States Patent and Trademark Office

In re Cederholm-Williams	:	BOARD OF PATENT APPEALS AND INTERFERENCES
Serial No.: 09/334,325	:	
Filing Date: June 16, 1999	:	
For: Fibrin Sealant As A Transfection/Transformation Vehicle For Gene Therapy	:	PATENT APPEAL
Docket No.: CV0276A	:	
Art Unit: 1632	:	
Examiner: Chen, Shin Lin	:	

APPELLANT'S APPEAL BRIEF

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1. **Real Party in Interest**

The inventors have assigned their interest to Bristol-Myers Squibb Company. Accordingly, Bristol-Myers Squibb Company is the real party in interest.

2. **Related Appeals and Interferences**

On information and belief, there are no other appeals or interferences that will directly affect or have a bearing on the Board's decision in this Appeal.

3. **Status of the Claims**

Claims 1, 2 and 13-16 are in the application. All other claims have been cancelled. All of the pending claims are subject to one or more rejections under 35 U.S.C. §§ 112, first paragraph, and 103(a). Claims 1, 2 and 13-16 are appealed.

4. **Status of Amendments Filed After Final**

No amendments to the specification or claims were submitted in the After Final response to the June 5, 2002 Office Action (Paper No. 18). Accordingly, the claims are in the form submitted in a response filed April 18, 2002. The pending claims are attached as Appendix A.

5. **Summary of Invention**

The invention relates to transforming cells with nucleic acid entrapped in fibrin used to maintain its contact with the cells targeted for transformation. Genetic transformation is a process whereby a cell acquires non-native genetic information and expresses it. In the present application, a transformed cell is defined as a cell where "a nucleic acid is recombinantly introduced into it or its ancestor so as to temporarily or stably (1) cause the cell to express a polypeptide or RNA in an amount not otherwise expressed by the cell or (2) interfere with the translation or transcription of a nucleic acid normally found in the cell." Specification at 21:6-9.

Thus, lead claim 1 is to:

A method of transforming a cell comprising the steps of:

applying a transformation effective amount of a nucleic acid to the cell;

adhering a pliable, adhesive fibrin gel to the cell so as to entrap a transformation effective amount of the nucleic acid in the fibrin gel adhered to the cell; and transforming the cell with the nucleic acid.

In a favored embodiment, the transformation uses a composition of fibrin stabilized in monomer form, which allows the polymer to be rapidly formed, helping to assure it acts to keep the nucleic acid in contact with the target cells. This embodiment is reflected in claims 15 and 16.

6. **Issues**

The issues are:

(a) Issue 1: Does the specification, and extensive knowledge in the art at the time of filing, enable one of skill in the art to transform a cell *in vivo* by applying a nucleic acid and a pliable, adhesive fibrin gel to said cell?

In one aspect, this issue is whether the applicant has enabled the invention. Notwithstanding, the basis of the rejection is an assertion that the application fails to demonstrate that the invention works. Thus, the 35 U.S.C. § 112 rejection is simply a rejection under 35 U.S.C. § 101 in the guise of a rejection under 35 U.S.C. § 112. Hence, the first issue addressed herein is whether the Office, when making a rejection such as this, can escape the constraints imposed by the case law of the Court of Appeals for the Federal Circuit on 35 U.S.C. § 101, or the Office's own arduously developed standards therefore, simply by framing the rejection as one under 35 U.S.C. § 112. Because it is respectfully submitted that the answer to the issue framed in the previous question is no, the rejection will be analyzed under the Office's Utility Examination Guidelines. Federal Register, Volume 66, Number 4, January 5, 2001. Last, the rejection will be analyzed under the precedent of the Court of Appeals for the Federal Circuit.

(b) Issue 2: Are claims 1, 2 and 13-16 obvious in view of the teachings of U.S. Patent No. 5,833,651 (Donovan)?

7. **Grouping of claims**

The rejection under 35 U.S.C. § 112, first paragraph, may be decided on the basis of claim 1. As to the analysis of the claims regarding the rejection under 35 U.S.C. § 103(a), claims 2 and 13-14 stand or fall with claim 1 and claims 15 and 16 must be separately analyzed for patentability. The additional limitations found in each of dependent claims 15 and 16 are not taught or suggested by the cited documents taken alone or in combination.

8. **Argument**

(a) **Rejection Under 35 U.S.C. § 112, First Paragraph - Enablement**

Claims 1, 2, and 13-16 stand rejected. The Office asserts that the rejection is for lack of enablement under 35 U.S.C. § 112, first paragraph, and is distinct from a rejection under 35 U.S.C. § 101 asserting inoperability. Specifically, the Office asserts that

> the specification, while being enabling for a method of transforming a cell *in vitro* by applying a nucleic acid and a pliable, adhesive fibrin gel to said cell, does not reasonably provide enablement for a method of transforming a cell *in vivo* by applying a nucleic acid and a pliable, adhesive fibrin gel to said cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims and is repeated for the reasons set forth in the preceding Official action mailed 12-19-01 (Paper No. 15). Applicant's arguments filed 4-18-02 have been fully considered but they are not persuasive.
>
> Applicant argues that it is well known in the art that *in vivo* transfection can give rise to immune response and there are more than sufficient vectors in the art which are not disabled in their effect by an immune response. Applicant further argues that vector-based vaccines were known and desirable and are enabled

(amendment, p. 2, 3). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 12-19-01 (Paper No. 15) and that the specification fails to provide adequate guidance and evidence to enable the use of nucleic acid and pliable, adhesive fibrin gel as a vaccine in the claimed method to stimulate immune response *in vivo*. No evidence of record indicates that the nucleic acid itself can stimulate sufficient immune response in a subject *in vivo* so as to provide therapeutic effect for a particular disease or disorder. In case that the protein product encoded by the nucleic acid is desirable to stimulate immune response *in vivo*, there is no evidence of record that indicates sufficient protein product is expressed in vivo to stimulate sufficient immune response *in vivo* for treating a particular disease or disorder. Thus, the specification fails to provide enabling disclosure for the use of nucleic acid and pliable, adhesive fibrin gel as a vaccine in the claimed method of stimulate immune response *in vivo*.

In fact, the intended use of the nucleic acid and pliable, adhesive fibrin gel is for gene delivery in *in vivo* gene therapy in light of the specification (see specification, p. 2-4). As discussed in the preceding Official action mailed 12-19-01 (Paper No. 15), host immune response poses problems to the use of various vector and virus in gene transfer *in vivo*. Further no teachings are present within the specification in regard to how to transform cells with any nucleic acid in any vector or any virus containing said nucleic acid by using fibrinogen composition or fibrin gel, **how the nucleic acid entrapped in fibrin gel can be taken up by cells**, and whether the nucleic acid taken up by cells can be expressed in said cells *in vivo*. Thus, the specification fails to provide enabling disclosure for the use of nucleic acid and pliable, adhesive fibrin gel for gene delivery *in vivo*. One skilled in the art at the time the of the invention would require undue experimentation to practice over the full scope of the invention claimed.

(Paper No. 18, p. 2-4)(emphasis added).

(i) The Rejection Fails to Conform to Office Guidelines

That the nature of the rejection focuses on the text presented above in added **bold** is clear from the text presented above in added underline. That is, the text in added underline acknowledges that the description of how to make the transforming composition is indeed in the application, and that transforming

nucleic acids are well-known. Implicit in this acknowledgement is that those of ordinary skill who have undertaken many transformations know how to measure for such transformation. What is left is what is emphasized in **bold**--the Office's assertion regarding the specification's teachings relative to how the nucleic acid entrapped in fibrin gel can be taken up by cells.

(ii) Can the Office Avoid the § 101 Structure of Analysis by Asserting Only the Sister Rejection under § 112?

The first question is whether, when the basis of the rejection is an assertion of inoperativeness, can the Office avoid the burden-shifting structures imposed by the courts and published Office policy merely by framing the rejection as a rejection under 35 U.S.C. § 112. The answer to this question is provided by the Court of Appeals for the Federal Circuit in In re Cortwright, 165 F.3d 1353, 49 USPQ2d 1464 (Fed. Cir. 1999). In Cortwright, the Board of Patent Appeals and Interferences reversed a rejection under 35 U.S.C. § 101, but imposed an analogous rejection under 35 U.S.C. § 112, first paragraph. The Federal Circuit implicitly accepted that the framing of the rejection under 35 U.S.C. § 112, first paragraph, was acceptable, but imposed exactly the same burden shifting procedure for analyzing the propriety of that rejection as would be imposed for a similar rejection under 35 U.S.C. § 101, citing the same precedent-setting cases relevant to § 101. Cortwright at 1356-57, 49 USPQ2d at 1466. Similarly, in In re Brana, the Federal Circuit reviewed a rejection for want of operativeness, made by the examining corps and the Board on the basis of 35 U.S.C. § 112, under the parameters developed for rejections under 35 U.S.C. § 101. 51 F.3d 1560, 1565, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995). Moreover, one of the earliest decisions relied upon by the courts as presenting the mode of analysis under § 101 was in fact decided with respect to 35 U.S.C. § 112. See In re Marzocchi, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971). Thus, it is clear that even though a rejection for want of operativeness implicates 35 U.S.C. §

112, the proper mode of analysis for such a rejection remains that set forth in the case law relating to 35 U.S.C. § 101.

(iii) The Rejection Fails to Conform to Office Guidelines

Because the subject rejection was for want of utility, it was incumbent on the Office to present sufficient reason to doubt Applicant's assertion of utility. One way to seek to conform to the legal requirements for such a rejection would be to follow the Office's own internal guidelines--the Utility Examination Guidelines. While the burden on the Office to justify an assertion of want of a credible utility would appear more relaxed in the guidelines than in the precedent of the Court of Appeals for the Federal Circuit, even this low hurdle was not met in the subject rejection.

The Office's Utility Examination Guidelines require:

> Any rejection based on lack of utility should include a detailed explanation why the claimed invention has no specific and substantial credible utility. Whenever possible, the examiner should provide documentary evidence (e.g., scientific or technical journals, excerpts from treatises or books, or U.S. or foreign patents) to support the factual basis for the prima facie showing of no specific and substantial credible utility. *If documentary evidence is not available, the examiner should specifically explain the scientific basis for his or her factual conclusions.*

(Guidelines at §B.3.). Applicant submits that the rejection does not specifically explain a scientific basis to doubt the Applicant's utility. To the contrary, in the making the subject rejection, the Office turns the burden, which the Office's own rules specifically places on itself, onto the Applicant, requiring proofs. For instance, the Office asks the Applicant to explain "how the nucleic acid entrapped in fibrin gel can be taken up by cells." Applicant respectfully notes that even the most skilled in the art can offer no more than informed speculation on the mechanism of transformation. Such is not a requirement of the patent law. That is, the patent law does not require an applicant to understand the theory of operation for his or her invention.

Implicit in the Office's assertion is a belief that the nature of a fibrin gel would somehow disable transformation. That *belief* is not shared by the Applicant. Moreover, the Office's

guidelines require that the Office explain any reasoning behind this belief, so that Applicant has a real opportunity to respond.

Moreover, according to the Guidelines, the Office's showing must contain the following:

> (1) An explanation that clearly sets forth the reasoning used in concluding that the asserted specific and substantial utility is not credible;
>
> (2) Support for factual findings relied upon in reaching this conclusion; and,
>
> (3) An evaluation of all relevant evidence of record, including utilities taught in the closest prior art.

(Guidelines at §B.3.(b).). In other words, the Office must tell the Applicant, in factually supported detail, why it believes that entrapping nucleic acid in fibrin will interfere with the transformation process. The Office's showing must, moreover, establish not that the Examiner believes that fibrin polymer interferes, but that "it is more likely than not that a person skilled in the art would not consider credible any specific and substantial utility asserted by the applicant for the claimed invention." Guidelines at §B.3.(b).

Accordingly, the subject rejection does not meet even the minimal requirements of the Utility Guidelines. Because, as will be seen, the amount of proof required to shift the burden to the Applicant under the guidelines is low, the Office's failure to meet this minimal requirement mandates a reversal of the subject rejection.

(iv) Legal Standard for Reversing the Burden Onto the Applicant

The Court of Appeals for the Federal Circuit has reiterated that:

> [A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of Section 112 unless

there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

Brana, at 1565, 34 USPQ2d at 1441 (quoting Marzocchi, at 223, 169 USPQ at 369). It is:

> *Only* after the PTO provides *evidence* showing that one of ordinary skill in the art would reasonably *doubt* the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility.

Brana, at 1565, 34 USPQ2d at 1441.

Thus, the Office must accept the Applicant's assertion of the usefulness of the invention *unless* it provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility, not mere speculation that an invention might not work.

(b) **Rejection Under 35 U.S.C. §103(a) - Obviousness**

(i) Argument as to all claims 1, 2 and 13-16

Claims 1, 2 and 13-16 stand rejected under 35 U.S.C. § 103(a) as assertedly unpatentable over the U.S. Patent No. 5,833,651. Specifically, the Office asserts that the '168 patent

> Applicant argues that Office action at page 6 suggest that Donavan teaches using fibrin other than using a tent is in error. Applicant further argues that the meaning of "fibrin monomer" is Donovan is different from that as defined in the specification (amendment, p.3). This is not found persuasive because of reasons of record. Donovan teaches the stent can be loaded with virus by mixing a solution of fibrin monomer and virus containing nucleic acid to form a polymer, i.e. fibrin gel, which can be used to deliver the virus to the cell at column 13. The Office does not imply that the mixture can be delivered to cell via apparatus other than stent. Donovan teaches using a **solution** of "fibrin monomer" which would indicates [sic] that the "fibrin monomer" is **non-polymerized** so that it is in a **solution**. Therefore, the term "fibrin monomer" in Donovan has the same meaning as that defined in the specification of the present application, i.e. stabilized in essentially non-polymerized form. It would be obvious and well known in the

art for how to stabilize "fibrin monomer" in a non-polymerized form.

Applicant argues that there is no teaching in Donovan to entrap nucleic acid adhered to a cell in a pliable fibrin gel and cites Winner International Royalty Corp vs Wang (amendment, p. 3, 4). This is not found persuasive because of reasons of record. It would have been obvious for one of ordinary skill at the time of the invention to apply a nucleic acid because adding a nucleic acid to cells before, during, or after the formation of a pliable, adhesive fibrin gel are for the same purpose of entrapping the nucleic acid in fibrin gel to deliver said nucleic acid to said cells and would be obvious for one of ordinary skill.

(Paper No. 18, pages 4-5).

The present application uses the term "fibrin monomer" with a specific meaning provided at page 19: the fibrin is stabilized in essentially non-polymerized form. Despite the Office's assertion, nothing in Donovan suggests or indicates such a meaning. Thus, the term "fibrin monomer" in Donovan has no implications as to the same words (with a clearly different meaning) recited in the specification.

Moreover, the Office in hindsight concludes what is not suggested in Donovan: that it would be desirable to entrap nucleic acid in a pliable fibrin gel adhered to a cell. But, the suggestion to modify must come from the prior art, not the comfort taken from the roadmap to the invention provided by the Applicant's specification.

To find motivation to modify in the prior art, that prior art must provide evidence that the combination or modification would have been viewed as desirable in the context of the prior art teachings. See, MPEP 2143.01. This desirability must be evidenced by more than a conclusion that the alleged combination is feasible. Id.

Relatively recently, in Winner International Royalty Corp. v. Wang, the Federal Circuit applied this desirability standard to uphold the validity of claimed subject matter where different references separately disclosed each element of a claimed invention. Winner, 202 F.3d 1340, 53 USPQ2d 1580 (Fed. Cir. 2000) (attached as Exhibit B-3), cert. denied, 530 US 1238. In Winner, the claims at issue were directed to a "Club"-like automobile anti-theft device locked in place across a steering wheel by a self-locking, ratcheting mechanism. References presented at trial

disclosed (1) a similar anti-theft device that used a dead-bolt mechanism instead of the ratcheting mechanism, (2) a "Y-shaped" anti-theft device mounted on the steering wheel that used a ratcheting mechanism and (3) other pedal-mounted anti-theft devices that can accommodate either a ratcheting or a dead bolt mechanism. Accordingly, the Federal Circuit found that the first reference disclosed "virtually all aspects claimed" except the ratcheting mechanism. Id. at 1349, 53 USPQ2d at 1587. The second reference disclosed the ratcheting mechanism and the third group of references "may have informed one of ordinary skill in the art that both mechanisms would work." Id. at n. 7. However, the references did not suggest that one mechanism *should* be replaced with another. Id. The Federal Circuit concluded that one of reasonable skill in the art may well have not elected to trade the superior security of a dead-bolt mechanism for the superior convenience of a ratcheting mechanism: "[t]rade-offs often concern what is feasible, not what is, on balance, desirable. Motivation to combine requires the latter." Id. at 1349, 53 USPQ2d at 1587. Accordingly, the Federal Circuit held that claimed device with ratcheting mechanism was not obvious under 35 U.S.C. §103. The Office provides no evidence of desirability.

Accordingly, as in Winner, one of skill in the art would not, based on the reference cited, find it desirable to entrap nucleic acid in a pliable fibrin gel adhered to a cell. The reference does not teach that it would have been desirable to do so. Accordingly, this rejection under 35 U.S.C. § 103 should be withdrawn.

(ii) Further argument as to claims 15 and 16

In addition to the foregoing, Appellant further respectfully submits that the cited art in no way discloses, suggests or provides any sort of motivation to take the extra steps of using fibrin monomer (which has nothing to do with Donovan's "monomer") or in particular acid-solubilized fibrin. Accordingly, this rejection under 35 U.S.C. § 103, particularly as it is applied to claims 15 and 16 should be withdrawn.

CONCLUSION

For the foregoing reasons, Appellant respectfully requests that the rejections under 35 U.S.C. § 112 and 35 U.S.C. § 103(a) with respect to all of the pending claims, namely claims 1, 2 and 13-16, be reversed and the pending claims in the application allowed.

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Appendices:

A: Claims on Appeal.

APPENDIX A - COPY OF CLAIMS ON APPEAL

1. A method of transforming a cell comprising the steps of: applying a transformation effective amount of a nucleic acid to the cell; adhering a pliable, adhesive fibrin gel to the cell so as to entrap a transformation effective amount of the nucleic acid in the fibrin gel adhered to the cell; and transforming the cell with the nucleic acid.

2. The method of claim 1, wherein the nucleic acid is applied in admixture with a fibrin or fibrinogen composition that forms the pliable, adhesive fibrin gel.

13. The method of claim 1, wherein the nucleic acid is a plasmid.

14. The method of claim 1, wherein the nucleic acid is incorporated in a virus.

15. The method of claim 1, wherein the pliable, adhesive fibrin gel is formed by mixing a fibrin monomer composition with a polymerizing agent preparation effective to convert the fibrin monomer preparation into a fibrin gel, and adhered by contacting the cell with the mixture while the mixture is pliable and adhesive.

16. The method of claim 15, wherein the fibrin monomer composition comprises acid-solubilized fibrin, and the polymerizing agent comprises an amount of base effective to sufficiently neutralize the mixture to allow the fibrin to polymerize.